Understanding and treating those irritating infections

CIRCADIAN CONTROL OF PRIMARY LUNG ALLOGRAFT DYSFUNCTION, MEDIATED BY THE CLOCK PROTEIN, REVERBα

Introduction

The circadian clock regulates murine immune responses by time of day, partly through the clock protein REVERBα, resulting in altered mortality after infection. The mechanisms regulating time of day differences are poorly understood in humans, where performing circadian studies presents a number of challenges. Lung transplantation, which is performed at any time of day to minimise organ ischaemic complications, had a previous lung transplant, or if the donor had undergone CTTA, was examined for an eight year retrospective cohort (n=563) in one centre. Patients were excluded, a priori, if they had significant intra-operative complications, had a previous lung transplant, or if the donor lung had undergone ex-vivo perfusion. Circadian factors were also studied using PER2::Luc and REVERBα mice and by pharmacological targeting of the circadian clock in primary alveolar macrophages from lung transplant recipients.

Methods

Primary graft dysfunction (PGD) incidence after lung transplantation was examined for a eight year retrospective cohort (2004–2012) cohort (n=563) in one centre. Patients were included, a priori, if they had significant intra-operative complications, had a previous lung transplant, or if the donor lung had undergone ex-vivo perfusion. Circadian factors were also studied using PER2::Luc and REVERBα mice and by pharmacological targeting of the circadian clock in primary alveolar macrophages from lung transplant recipients.

Results

The incidence of PGD grades 2/3 at 24 hours was temporarily elevated when organs were reperfused between 4 and 8 am (p<0.02) compared to other time points. Similar observations were made when the cohort was examined by operation start time (p<0.01). Sub-cohort analysis, defined using ISHLT relative contraindications, revealed that PGD incidence oscillated in a circadian manner (r²=0.87, p=0.046). Investigations in PER2::Luc mice, which allows real time tracking of circadian oscillations, revealed that temperature and serum fluctuations, mimicking organ preservation, shifts the donor organ clock by 4–12 hours depending on time of retrieval. This could create circadian desynchrony between the transplanted organ and recipient. In macrophages, genome-wide gene expression analysis of the role of REVERBα identified gene ontology terms linked to the regulation of lymphocyte function and activation, suggesting a functional link from the macrophage to the adaptive immune response. Furthermore, key PGD biomarkers were elevated (p<0.05) in macrophages from REVERBα mice and were repressed (p<0.05) by REVERB ligands (GSK2945 and GSK2667) in macrophages from lung transplant recipients.

Conclusion

This study suggests that the circadian clock could temporarily affect outcomes after lung transplantation due to recipient-donor circadian desynchrony. Ligands targeting the clock protein REVERBα repress key PGD biomarkers showing that this is a tractable therapeutic pathway.